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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Patent Application of:	Joanne Y. H. Kwak-Kim et al.
For:	DIAGNOSIS AND TREATMENT OF INFERTILITY
Serial No.	10/651,690
Filed:	August 28, 2003
Examiner:	Michael E. Szperka
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CERTIFICATE OF MAILING

I hereby certify that this paper is being deposited with the United States Postal Office with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on May 23, 2006.

Tin-Chuen Yeung

COMBINED DECLARATION OF JOINT INVENTORS UNDER 37 C.F.R. §131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Joanne Young Hee Kwak-Kim, M.D. and Alice Gilman-Sachs, Ph.D. aver as follows:

1. We are over the age of twenty-one years and make these statements from our own personal knowledge.

2. I, Dr. Kwak-Kim currently hold the position of the Assistant Chair, Department of Obstetrics and Gynecology; and the Medical Director, the Clinics at Rosalind Franklin University of Medicine and Science; and the Director, Women's Health Division, University Clinics; and Associate Professor, Department of Obstetrics and Gynecology and the Department of Microbiology and Immunology of the Rosalind Franklin University of Medicine and Science (formerly known as Finch University of Health Sciences)/The Chicago Medical School.

3. I, Dr. Gilman-Sachs, currently hold the position of Associate Professor of the Rosalind Franklin University of Medicine and Science (RFUMS) and also hold the position of Associate Director Clinical Immunology Laboratory for RFUMS.

4. We are both joint inventor of the above-captioned patent application.

5. Joint inventor Alan E. Beer is deceased.

6. Prior to April 19, 1999 we planned to study the affect on reproductive outcomes, in subjects with a history of recurrent spontaneous abortions or implantation failures, by adjusting the balance of T helper 1 (Th1) and T helper 2 (Th2) immune responses in the subject. A letter signed by Dr. Kwak-Kim with the date expurgated is attached as Exhibit 1 and was mailed prior to the Critical Date. In particular, we determined to decrease the ratio of Th1 immune response to Th2 immune response by either (a) down regulating the Th1 immune response, (b) by up regulating the Th2 immune response or (c) by both down regulating the Th1 immune response while up regulating the Th2 immune response.

7. Further to this planned study, prior to the Critical Date we began development of an assay to measure the ratio of Th1 to Th2 immune responses in a subject. We have attached as Exhibit 2 a set of laboratory notebook pages with dates removed evidencing the development of the assay. The ratio of the Th1 to Th2 immune responses can be measured by absolute cell counts or percentage of Th1 cells to Th2 cells. Th1 cells are the activated T-cells expressing Th1 cytokines such as IL-1, IL-2, IFN-γ and TNF-α. Th2 cells are the activated T-cells expressing Th2 cytokines such as IL-4, IL-5, IL-6 and IL-10. The ratio of the Th1 to Th2 immune responses can also be determined by calculating a ratio of any one of the Th1 cytokines to any one of the Th2 cytokines.

8. One method we contemplated to reduce the Th1 count was to administer to a subject, prior to conception by the subject, a TNF-α antagonist. TNF-α antagonist may be of several types including antibodies, soluble receptors, and chemical compounds. We contemplated using several commercially available TNF-α antagonists and TNF-α antagonists that were undergoing an FDA approval process in the hope of becoming commercially saleable. Examples of antibody type and soluble receptor-type TNF-α antagonists included, but were not limited to: (1) infliximab (antibody-type) (2) entanercept (soluble receptor-type) (See Exhibit 1), (3) D2E7 (antibody-type) (4) CDP571 (antibody-type) and (5) CDP870 (antibody-type).

9. We contemplated administering the TNF-α antagonist by any medically suitable route of administration.

10. After conceiving of these concepts we worked on them diligently from prior to the Critical Date up to the time of filing the above-captioned patent application.

11. All of the work we have referred to herein was done in the United States of America.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, I acknowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and may jeopardize the validity of the application or any patent issuing thereon.

Date: 5/17/2006 BY Joanne Kwak-Kim

Dr. Joanne Kwak-Kim

Date: 5/17/2006 Alice Gilman-Sachs

Dr. Alice Gilman-Sachs